REMARKS

The Examiner has indicated that Document AM was not previously received. Thus, enclosed herewith is a copy of the reference indicated under AM. Enclosed herewith is a new PTO-1449 from which includes all of the proper bibliographical information.

The Examiner has indicated that the priority references were in Italian and thus a translation is required. Please note that included herewith is a translated copy of Italian Patent Application RMA000306 filed on June 5, 2000. A translation of MI99A001783 will be filed just as soon as it is completed.

The specification and drawings have been objected to as the figure labels are in Italian and panel F has not been described in the specification. Please note that these are being translated and will be amended once the application has been allowed.

Claims 1, 4-6, 7-9, 12 and 19 have been objected to due to minor informalities. The claims have been amended to obviate the Examiner's objection.

The application has now complied with the requirements of 37 C.F.R. 1.821 through 1.825. Thus, enclosed herewith is a computer readable copy of the sequence listing, a paper copy of the sequence listing and a statement that the paper and computer readable copies are the same and no new matter is included.

Claims 2, 4-10 and 14 have been rejected under 35 U.S.C. §112, second paragraph. The claims have been amended to obviate the Examiner's rejection.

Claims 1-19 have been rejected under 35 U.S.C. §112, first paragraph. The claims have been amended to obviate the Examiner's rejections.

Claims 1-19 have been rejected under 35 U.S.C. §102 a as being anticipated by Ruberti et al. (J. Neurosci 20(7): 2589-2601, 4/2000), as evidenced by Ruberti et al. (Cell. Mol. Endocrinol. 13(5): 559-568, 1993). Claims 1-19 have been rejected under 35 U.S.C. §102(a) as being anticipated by Capsoni et al. (Proc. Nat. Acad. Sci. USA 97(12): 626-6830, 2000) as evidenced by Ruberti et al. (J. Neurosci 20(7): 2589-2601, 4/2000)

The Examiner's rejection is respectfully traversed.

The publication of Ruberti et al. was published April 1, 2000 after the filing of the earliest priority of application MI99A001783 which was filed August 6, 1999. Claims 1-19 are fully based on the priority of this reference and therefore are not anticipated by Ruberti et al., 2000. The same applies for the publication of Capsoni et al. as it was published in February 2000. The publication of Capsoni et al. (PNAS 97(12)) was published in June of 2000. Again, all three references were published after the initial priority application filing date of August 6, 1999. Claims 1-19 are all based on this priority, and thus, the three rejections should be withdrawn.

Claims 1-3, 17 and 18 have been rejected under 35 U.S.C. §102(b) as being anticipated by Piccioli et al. (Neuron 15: 373-384, 1995).

The Examiner's rejection is respectfully traversed.

The claims as now amended are directed to non-human transgenic animal being transgenic for anti-NGF antibody, having a phenotype reminiscent of a human neurodegenerative syndrome, muscular atrophy or dystrophy or immune disorder.

The publication of Piccioli et al., (Neuron 15:373-384, 1995) refers to the production and analysis of transgenic mice expressing anti-substance P (SP) antibodies. The mice were analyzed

for acute nociception, neurogenic inflammation, and motor and exploratory behavior. The results indicate that anti-SP mice present motor deficits as measured by the number of lines crossed in a ten minute open field test. This publication does not include any histological data demonstrating the presence of muscular atrophy. It is indicated in the publication that further investigations are needed to clarify the molecular mechanism and the precise site of action of such observation, see p.381, right column, bottom of first paragraph.

By contrast, anti-NGF mice display normal locomotor activity in the open field test while motor deficits are detected in a rotarod experiment, which has not been conducted in anti-SP mice. A person skilled in the art would understand that the open field which is a simple apparatus assesses hyperactivity, exploratory activity, and stereotyped rotation while the rotarod assay investigates motor coordination, balance, and motor learning.

In addition, Piccioli et al., do not link the phenotype observed in anti-SP transgenic mice to any human pathology in particular to Alzheimer's disease. Therefore, the claims are not anticipated by Piccioli et al.

Claims 1-18 have been rejected under 35 U.S.C. §102(b) as being anticipated by Cattaneo et al.(Society for Neuroscience Abstracts 22 (1-3): 753,1996).

The Cattaneo et al. reference describes a family of AD11 mice (Family A) that is not described in the present patent application. Family A is different from the AD11 family 1 and 2 described in the present application in the following points and as summarized in Table 1.x.

A) Crossing

Family A derives from breeding AD11–VH mice expressing low levels of the transgenic chain VH (line C) to AD11-VK mice expressing low levels of the transgenic chain VK (line A). The two families described in the present application were obtained as follow:

Family 1 is obtained by crossing AD11-VH mice expressing high levels of the transgenic chain VH (line D) to AD11-VK mice expressing low levels of the transgenic chain VK (line A).

Family 2 is obtained by crossing AD11-VH mice expressing low levels of the transgenic chain VH (line C) to AD11-VK mice expressing high levels of the transgenic chain VK (line B).

B) Levels of antibodies

Family A (like families 1 and 2) is characterized by the lack of detectable functional antibodies during the first month of age. After 1 month of age, the levels of antibodies start to be detectable, but at a significantly lower level with respect to family 1 and 2. Indeed, while the levels of antibody at postnatal day 45 in family 1 and 2 are already 50-300 ng/ml and remain stable thereafter, whereas in family A the levels of antibody at 30- 45 days of age are around 10 ng/ml, remain at this level for a few months thereafter and reach the amount of 50-100 ng/ml only after 12 months of age.

C) Phenotype

The AD-like phenotype is completely absent in Family A. Please see graphs in which the authors show the absence in family A:

i) of cholinergic deficit (enclosed Fig. 1, and corresponding legend below),

ii) of beta amyloid deposition (enclosed Fig. 2, and corresponding legend below)

iii) of the accumulation of phosphorylated tau (enclosed Fig. 3, and corresponding legend below).

The only detectable change with respect to wild type mice is a shrinkage of the superior cervical ganglia (enclosed Fig. 4, and corresponding legend below).

Figure Legends

Fig. 1. Neurostereological counts to determine the total number of cholinergic neurons in the basal forebrain (BF) of WT mice, AD11 family 2 and AD11 family A mice. AD11 family 2 mice show a decrease in the number of cholinergic neurons with respect to WT mice (* $P < 0.05$), while AD11 family A do not differ from WT mice and are statistically significant different from AD11 mice family 2 (# $P < 0.05$).

Fig. 2. Counts to determine the number of Abeta clusters and plaques in the hippocampus of WT mice, AD11 family 2 and AD11 family A mice. AD11 family 2 mice show an increased number of plaques with respect to WT mice (* $P < 0.05$), while AD11 family A do not differ from WT mice and are statistically significant different from AD11 mice family 2 (# $P < 0.05$).

Fig. 3. Neurostereological counts to determine the total number of phosphotau neurons in the entorhinal cortex of WT mice, AD11 family 2 and AD11 family A mice. AD11 family 2 mice show a decrease in the number of phosphotau-positive neurons with respect to WT mice (* $P < 0.05$), while AD11 family A do not differ from WT mice and are statistically significant different from AD11 mice family 2 (# $P < 0.05$).

Fig. 4. Superior cervical ganglia (SCG) in AD11 Family A. (a) Coronal section through the center of SCG of wild type mouse. (b) Coronal section through the center of SCG of Family A

mouse. The loss of neurons in transgenic mice results in a reduction in the total area of the ganglion.

Table 1: Difference between transgenic family A (Cattaneo et al.,) and family 1 and 2 (present application)

Family	Crossing		Antibody levels At day 45 (ng/ml)	AD-like phenotype
	AD11-VH	AD11-VK		
A	Line C Low level of VH	Line A Low level of VK	10	absent
1	Line D High level of VH	Line A Low level of VK	50-300	present
2	Line C Low level of VH	Line B High level of VK	50-300	present

Claims 1 and 17-19 have been rejected 35 U.S.C. §103(a) as being unpatentable over Cattaneo et al. in view of Hogan et al. (In *Manipulating the Mouse Embryo*, Cold Sring Harbor Laboratory, Cold Spring Harbor, NY, pg. 81, 1986).

The Examiner's rejection is respectfully traversed.

Cattaneo et al., 1996 suggest that the process of creating a transgenic mice line for aD11 heavy chain (line Z), creating a transgenic mice line for aD11 light chain (line Y), and crossing

line Z with line Y would generate animals having circulating antibody levels of 50-100 ng/ml in adulthood and having a 30 % reduction of neurons in the superior cervical ganglia, while Hogan et al. teach a general procedure to manipulate mouse embryo.

Therefore, a person skilled in the art would not have predicted from Cattaneo et al. 1996 in view of Hogan et al. to obtain a transgenic mice having the following phenotype:

1) dilation of the cerebral ventricles,

2) atrophy of the cerebral cortex, sometimes associated with the complete disappearance of the hippocampus,

3) loss of neurons and/or neuronal apoptosis,

4) deposition in the CNS of plaques of β-amyloid protein, at level of the cerebral cortex, neostriatum, hippocampus,

5) neurofibrillar tangles and dystrophic neurites in the brain,

6) aggregation of the tau protein in the brain,

7) cognitive deficits characterised by defects in the «working memory» and spatial orientation deficits,

8) cholinergic deficit,

9) hyperphosphorylation of the tau protein at cerebral level,

10) dystrophy of skeletal muscles, particularly at level of the rear limbs,

11) deposition of plaques of β-amyloid protein in the skeletal muscle,

12) hyperphosphorylation of the tau protein in the muscle,

13) infiltration of inflammatory cells in the muscle,

14) modifications of the sympathetic innervation of the spleen and reduction of the splenocyte viability.

Moreover, a person skilled in the art could not foreseen that such phenotype could be obtained by crossing single transgenic lines having either high level of Vh or high level of VK (as for family 1 and 2).

In view of the foregoing, it is believed that the amended claims and the claims dependent there from are in proper form. The Applicants respectfully contend that Ruberti et al, Capsoni et al, (both citations) Piccioli et al or Cattaneo et al, do not anticipate the claimed invention under the provisions of 35 U.S.C. § 102 and Cattaneo et al. in view of Hogan et al. do not render the Applicants' invention as obvious under the provisions of 35 U.S.C. §103(a). Thus, claims 1-19 are considered to be patently distinguishable over the prior art of record.

The application is now considered to be in condition for allowance, and an early indication of same is earnestly solicited.

Respectfully submitted,

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